RESIDUAL SEDATING EFFECTS OF ETHANOL

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Summary. Sixty, healthy young men (mean age 25.6 yrs) consumed either ethanol (0.40, 0.60, 0.75 and 0.80 g/kg) or placebo at 0900-0930 h after spending 8 hrs time-in-bed (TIB) the previous night. Latency to sleep onset (on the Multiple Sleep Latency Test, a standard measure of daytime sleepiness/alertness) was tested at 1000, 1200, 1400 and 1600 h. Ethanol reduced average daily sleep latency (for the four tests) compared to placebo in a dose related manner. Breath ethanol concentration (BEC) 30 min post ingestion differed significantly among ethanol doses and showed a significant reduction with time since ingestion. Sleep latency, when analyzed for time effects, did not show significant effects of time after ethanol administration. When BEC was zero at 1600 h, sleep latency still was significantly reduced on the ethanol day compared to the placebo day.

Key Words: ethanol, sleepiness, MSLT, residual sedation

Introduction

A number of studies have examined the sedating effects of ethanol using a direct objective measure of sleepiness/alertness. This measure, the Multiple Sleep Latency Test (MSLT), consists of four or more tests of the latency to achieve polygraphic signs of sleep at two-hour intervals throughout the day (Carskadon & Dement, 1982). The MSLT has a high test-retest reliability (Zwyghuizen et al, 1988a). Its validity has been established in a variety of experimental manipulations and clinical conditions with the results showing that sleepy persons consistently go to sleep more quickly than do alert persons (Roth et al, 1989).

Administration of ethanol (0900-0930 h) to healthy normal subjects reduces average daily sleep latency compared to placebo on tests conducted at 1000, 1200, 1400 and 1600 h (Zwyghuizen et al, 1988b; Zwyghuizen et al, 1988c; Roehrs et al, 1989). When latencies are analyzed test-by-test significant ethanol effects on sleep latency are found on each test. That is reductions in sleep latency relative to placebo are seen even after ethanol is no longer detectable in breath. This same phenomenon of residual sedation also has been reported recently from another laboratory with nighttime rather than daytime administration of ethanol (Walsh et al, 1989).

At present no paper has compared the sedating effects of ethanol to placebo across a range of ethanol doses, particularly with regard to the production of residual sedation. This paper presents data gathered in a number of studies done in this laboratory in which ethanol at different doses or placebo was administered at 0900-0930 h after 8 hrs in bed the previous night and sleep latency was tested from 1000-1600 h.

Method

Subjects

Sixty healthy, young men, aged 21-34 yrs, who reported drinking between 1 and 12 alcoholic drinks per week participated in the various studies. For
screening in all studies, the subjects had a physical examination, laboratory
tests, and a nocturnal (2300-0700 h) sleep recording followed the next day by a
MSLT conducted according to standard procedures. The screening requirements
are described below. Each subject signed an informed consent and was paid for
participation.

Procedure

The general methodology has been consistent between studies. In a
preliminary telephone screen each subject reported averaging 6.5-8 hrs of sleep
a night, regular bedtimes and times of arising (not varying by >2 hrs), no
difficulty sleeping, and no daytime sleepiness or habitual napping. They also
reported no use of psychoactive drugs, both licit and illicit. They received a
physical examination and standard laboratory tests with the results all within
normal limits. A urine drug screen was used to confirm the absence of
psychoactive drugs.

To establish normal nocturnal sleep and daytime sleepiness subjects
underwent nocturnal and daytime polysomnography. In both the nocturnal sleep
and daytime screening, electrodes were attached for standard monitoring and
sleep stage scoring (in 30-sec epochs) of tracings derived from monopolar EEG
(at central and occipital placements), electrooculogram from right and left
outer canthi, and chin electromyogram from the submental muscle (Rechtschaffen
& Kales, 1968). On the nocturnal screening subjects were required to have
sleep efficiencies (sleep time per TIB) of greater than 85%.

The following day, subjects were tested for level of sleepiness at 1000,
1200, 1400, and 1600 h using the standard MSLT procedures (Carskadon et al,
1986). For these and all subsequent latency tests subjects were placed in beds
in quiet, darkened rooms and instructed to close their eyes, relax, and try to
fall asleep. The MSLT was terminated at two consecutive epochs (30 sec) of
stage one sleep, the first signs of stage two or REM sleep, or 20 min of
continuous wake. Subjects with a mean sleep latency (on the MSLT) the
following day of >10 min were admitted to the various studies. Healthy normal
adults on such a screening usually have MSLT latencies of 10-15 min on average
(Roth et al, 1989).

After screening, subjects consumed ethanol (0.40, 0.60, 0.75 and 0.80
g/kg) and placebo in the various studies. Given this analysis is being done
across studies subjects were not randomly assigned to ethanol doses and the "n"
per dose is unequal. The "n" per dose is 0.4 g/kg = 10, 0.6 g/kg = 31, 0.75
g/kg = 9, and 0.8 g/kg = 10. Ethanol and placebo within a given study were
always presented in a counterbalanced order on each of two mornings (0900-0930
h) after an 8 hr TIB the previous night. The ethanol used was 80 proof
vodka, mixed 1:4 with tonic water, and flavored with lemon or lime juice. The
placebo consisted of the flavored tonic water with three drops of ethanol
floating on the surface. The ethanol consumption was done in a nonsocial
environment and drinking was paced over the 30 min period. Breath ethanol
concentration (BEC) was measured (Alcotest 7010, National Drager) each day at
1000, 1200, 1400, and 1600 h prior to the sleep latency tests.

Throughout each study subjects were instructed to avoid all outside
ethanol as well as caffeine-containing foods and beverages. They were also
instructed to maintain their regular exercise regimen during the study and to
avoid all drug use (prescription, illicit, and over-the-counter) one week before the study and during the study. Subjects avoided eating more than the required breakfast until after the 1200 h latency test, were monitored to ensure wakefulness between tests, and were asked to avoid napping during the study.

The dependent measures average daily sleep latency (min), sleep latency on each latency test, and BEC at each determination were each submitted to two or three factor (dose, ethanol versus placebo, and time where appropriate) analyses using the general linear models multivariate analysis of variance (SAS Institute) followed by Duncan post hoc comparisons where appropriate. A mixed design model was used with ethanol versus placebo as the within subject factor (in three factor analyses time was also within subjects) and ethanol dose as a between subject factor. The SAS general linear models analysis corrects for the unequal "n" per group. Conservative p levels corrected by the Greenhouse-Geisser procedure were used and effects of p<.05 or less are reported.

Results

Breath Ethanol Concentration (BEC)

BEC for each ethanol dose at each determination is presented in Table 1. The analysis comparing ethanol dose and time produced a significant dose effect (F=33.83, p<.001). In the post hoc comparisons the .4 g/kg dose differed from the .6, .75, and .8 g/kg doses, the .6 g/kg dose differed from the .75 and .8 g/kg dose, and the .75 and .80 g/kg were similar. A significant time effect was also found (F=392.89, p<.001) and the post hoc comparisons showed BEC at each determination differed from the previous level. Finally, a dose by time interaction was observed (F=12.56, p<.001) with the two lower doses reaching zero at 1400 h and all doses being zero at 1600 h.

Sleep Latency

The overall sedating effects of ethanol as a function of dose are presented in Figure 1. Average daily sleep latency for each ethanol dose was compared on the placebo versus the ethanol day. Average latency was reduced significantly on the ethanol days compared to the placebo days (F=81.87, p<.001). There was no main effect of dose, but there was a significant days by dose interaction (F=3.17, p<.03). Post hoc comparisons revealed no dose differences in average sleep latency on the placebo day. On the ethanol day latency for each of the ethanol doses differed from that on the placebo day and the low dose differed from the high dose with the two remaining doses being intermediate.

Analyses of time of day (or time since ethanol ingestion on the ethanol day) effects were also conducted. Sleep latency at each test (1000, 1200, 1400, and 1600 h) on placebo and ethanol days is presented in Table 2. On the placebo day there were no dose differences or a dose by time interaction. Consequently, means across the dose groups are presented in Table 2 for the placebo day data. On the placebo day there were significant time of day effects (F=3.10, p<.03). Latency on the 1000 h test differed from the latencies on the 1200 h and 1400 h tests, but not the 1600 h test.

Unlike the BEC data and the placebo day sleep latency data, in the ethanol
day analysis there were no time or time by dose differences in sleep latency. There were significant main effects of ethanol dose as was found for average sleep latency with the same pattern of dose differences. Since, the specific focus of this study is on residual sedation, that is sleep latency at that time when BEC was zero for all doses, an analysis was conducted on the 1600 h latency data alone. The results showed a significant main effect of (ethanol versus placebo) days ($F=15.50$, $p<.001$). However, no dose effects or days by dose interaction were observed.

Discussion

The analyses presented in this paper indicate that across ethanol doses consistent dose by time interactions for BEC were found. On the other hand, the sleep latency data did not show dose by time interactions; significant ethanol associated sedation was seen on each test. Thus ethanol associated reductions in sleep latency did not relate to the time course of BEC. At 1600 h when BEC had reached zero for all ethanol doses significant sedation remained. We have chosen to call this phenomena residual sedation.

The observation of residual sedation raises a number of intriguing issues. A determination as to how ethanol dose is related to the intensity and duration of the residual sedation is necessary. In all of these previous studies assessment was done only at two hours after BEC was zero for all doses and the present analysis showed no strong dose differences in residual sedation. Dose differences may be seen when multiple tests are conducted after zero BEC. Furthermore, the previous studies have not assessed performance at that point in time when residual sedation has been observed.

The residual sedation of these daytime studies seems to contradict the data from studies of the effects of ethanol on nighttime sleep (Williams & Salamy, 1972). Such studies typically administer ethanol in doses sufficient to raise BEC to 50-100 mg% just prior to sleep and they then record sleep continuously for 8 hrs. Signs of increased sedation are observed during the initial hours of the sleep period, but depending on the dose a subsequent increase in wakefulness and fragmentation of sleep is seen in the latter hours of the sleep period. Given the doses administered in these studies one would predict that BEC is zero during the latter hours of the sleep period. Hence, when BEC is probably zero in these nighttime studies, increased wakefulness (i.e. alertness) and not residual sedation is observed. The one nighttime study using the MSLT administered ethanol prior to subjects' usual bedtime, but then kept subjects awake (Walsh et al, 1989). Increased sedation relative to placebo on the MSLT was observed and residual sedation when BEC had reached zero was also reported. The differing results may be due to the fact that sleep was obtained in the earlier nighttime studies, while in the MSLT studies subjects remain awake. Thus, the residual sedation may be the expression of an unresolved sleep drive. If so, one would predict that sleep (a nap) should reverse the sedation following ethanol. Preliminary data suggest that a nap does reverse the sedation (Zwyghuizen et al, 1989).

Another interesting issue is whether this phenomena is unique to ethanol or whether other sedating drugs when administered to waking individuals will also show residual sedation when plasma concentrations of the drug approach zero. In addition to ethanol, the benzodiazepines and some of the $H_1$
antihistamines have been shown to have sedating effects using MSLT methodology. Given that these drugs are thought to produce sedation through different pharmacological mechanisms, the presence of residual sedation with these other drugs would suggest residual sedation is a secondary effect of the drugs produced through some final common mechanism. And if so, will sleep (a nap) similarly reverse the sedation of these other drugs? Studies addressing these issues are currently being conducted.

Acknowledgements

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References


### Table 1

<table>
<thead>
<tr>
<th>Breath Ethanol Concentration (BEC)</th>
<th>g/kg</th>
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<tr>
<td>Dose</td>
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<td>1000 h</td>
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<tr>
<td></td>
<td>(0.01)</td>
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Data are means and (standard deviations).

### Table 2

<table>
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<tr>
<th>Sleep Latency (min) on Each Test</th>
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<td>1200 h</td>
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<td></td>
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<td></td>
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<tr>
<td>1600 h</td>
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<tr>
<td></td>
<td>(5.68)</td>
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Data are means and (standard deviations)
Figure 1. Average daily sleep latency (min) on the placebo and the ethanol days for each ethanol dose.